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Gonadotropin releasing hormone (GnRH) agonists and the risks of diabetes and cardiovascular disease in men with prostate cancer

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Abstract

Androgen deprivation therapy (ADT) accomplished by either a gonadotropin releasing hormone (GnRH) agonist, GnRH antagonist, or bilateral orchiectomy is a common treatment for prostate cancer, the most common cancer in men. Given that most men diagnosed with prostate cancer will not die as a direct result of their prostate cancer, competing health risks are an important consideration. Several adverse metabolic effects of ADT have recently been described. The potential benefits of ADT in any given clinical setting must therefore be weighed against the potential harms. In October 2010, the United States Food and Drug Administration (FDA) released a safety announcement warning about increased risk of diabetes and cardiovascular disease due to GnRH agonist treatment, though these effects likely would result from any intervention that causes castrate testosterone levels. This commentary briefly summarizes the existing literature and provides perspective on its application to clinical practice. We advocate the adapted use of existing guidelines designed to manage the risks for diabetes and cardiovascular disease in the general population.

Keywords

prostate cancer; androgen deprivation therapy; GnRH agonists; diabetes; coronary artery disease

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Background

The adverse metabolic effects of ADT have only recently been described.[1] In May 2010, the United States FDA released a safety communication regarding GnRH agonists and possible increased risk of diabetes and certain cardiovascular diseases. In October 2010, the FDA then released a safety announcement requiring the manufacturers of GnRH agonists to add new information to the *Warnings and Precautions* section of the drug labels (http://www.fda.gov/Drugs/DrugSafety/ucm229986.htm#safety). They specifically require warning of increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.

ADT is clearly beneficial in some clinical settings. GnRH agonist therapy improves survival when combined with external beam radiation for the management of intermediate or high risk localized or locally advanced prostate cancer.[2–7] In addition, ADT palliates pain and modestly improves survival when given for metastatic prostate cancer.[8] Finally, ADT improves survival in men who are found at the time of prostatectomy to have nodal metastases.[9] Potential benefits of ADT in other clinical settings are less well defined. In all circumstances, it is important to weigh potential benefits against potential harms.

The FDA safety review focused on seven published studies that compare clinical outcomes among men with prostate cancer who are managed with or without ADT.[10–16] As the metabolic side effects of GnRH agonists are a result of castrate testosterone levels, it is likely that bilateral orchiectomies and GnRH antagonists cause similar risks. Six of the seven analyses demonstrate some significant association between ADT and the clinical outcomes studied. The FDA announcement states that synthesis of those studies suggests that GnRH agonist treatment is associated with a small increased risk for diabetes, myocardial infarction (MI), stroke, and sudden cardiac death. The agency has advised several specific guidelines regarding GnRH agonist use (see Table 1). The authors here provide a focused review of the relevant medical literature and perspective on its application to clinical practice. For a more exhaustive review of the topic, the reader is directed to the previously-published science advisory issued jointly by the American Heart Association (AHA), American Cancer Society (ACS), and American Urological Association (AUA).[17]

Metabolic effects of GnRH agonists

Several metabolic consequences of GnRH agonists have been prospectively and reproducibly described. First, GnRH agonists adversely affect body habitus, as they cause lean body mass to fall, fat mass to rise, and overall weight to rise.[18] [19] [20, 21] These changes tend to disproportionately increase abdominal subcutaneous fat,[18] [22] and they have been observed as early as three months after initiation of treatment.[23]

Second, GnRH agonists cause changes in serum lipid profile that include increases in triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).[18, 24–26] Significant changes in serum lipid profile can be observed within 3 months of initiation of therapy.[23, 24]

Finally, GnRH agonists decrease insulin sensitivity.[23, 24, 27] GnRH agonist-associated declines in insulin sensitivity have been prospectively demonstrated as early as 12 weeks after initiation of ADT among non-diabetic men.[23]

Type 2 diabetes

GnRH agonists cause weight gain and a decline in insulin sensitivity. Obesity and insulin resistance are both associated with type 2 diabetes in the general population.[28] Consistent

with these treatment-related effects, three notable population-based studies have identified significant associations between GnRH agonist treatment and a 16 – 44% elevated incidence of diabetes.

The first of those studies examined a Surveillance, Epidemiology and End Results (SEER)-Medicare database that included 64,721 men age ≥ 66 who had been diagnosed with locoregional prostate cancer and had no pre-existing diabetes.[12] Within that group, 36% of the men received a GnRH agonist and 7% underwent bilateral orchiectomy. With median follow-up of 4.55 years, new diagnoses of diabetes were more common among men treated with a GnRH agonist than in those not treated with ADT (adjusted hazard ratio (aHR) 1.44; $P < 0.001$). New diagnosis of diabetes was also more common in those who underwent orchiectomy, highlighting the fact that this is likely a consequence of castrate testosterone levels rather than an effect that is specific to GnRH agonists.

A matched cohort study using an Ontario, Canada database also reported a significant association between ADT and diabetes.[16] Almost 20,000 men age ≥ 66 who were treated with ADT (bilateral orchiectomies or ≥ 6 months of medical castration) were matched with men who had been diagnosed with prostate cancer but who were not treated with ADT. They found that ADT was associated with an increase in the risk of diabetes (HR 1.16, 95% CI 1.11 – 1.21).

This association was also demonstrated in an observational study of 22,356 men diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration without pre-existing diabetes.[11] In that study, GnRH agonist therapy was associated with a significantly elevated risk for incident diabetes (adjusted HR 1.28, 95% CI 1.19 – 1.38).

Cardiovascular disease

ADT causes weight gain, adverse changes in serum lipids, and insulin resistance. It is associated with an increased risk of diabetes. These metabolic consequences of GnRH agonists have prompted concern that there is an association between GnRH agonist treatment and cardiovascular disease (CVD) including MI, stroke, and sudden cardiac death. The currently available literature on this topic offers conflicting results.

Subheading: Population-based studies

Keating et al hypothesized that there would be an association between GnRH agonist treatment and CVD.[12] They performed a population-based analysis that included 73,196 Medicare enrollees age 66 or older who had been diagnosed with locoregional prostate cancer. They found that men who received GnRH agonist treatment were significantly more likely to be subsequently diagnosed with incident coronary heart disease (CHD; HR 1.16), MI (HR 1.11), and ventricular arrhythmias/sudden cardiac death (HR 1.16).

Saigal et al similarly conducted a retrospective analysis of almost 23,000 men from the SEER-Medicare database who had been diagnosed with prostate cancer. They found that at one year there was a 20% higher risk for serious cardiovascular morbidity among those treated with ADT.[13]

Van Hemelrijck et al assessed the association of ADT with CVD using a population-based database of prostate cancers in Sweden, a 76,600 patient database encompassing 96% of prostate cancer cases in the country.[15] They compared standardized incidence ratios (SIRs) and mortality ratios for ischemic heart disease, acute MI, arrhythmia, heart failure, and stroke for men with prostate cancer receiving different treatments with men in the general Swedish population. Men with prostate cancer were categorized as receiving

primary endocrine therapy (otherwise known as ADT) (40.0%), curative therapy (34.5%), and surveillance (25.5%). They found that the SIRs for MI were elevated in all three groups relative to the general Swedish population but were the highest with endocrine therapy (1.40 for endocrine therapy, 1.15 for curative therapy, and 1.20 for surveillance). For each 1,000 person-years of endocrine therapy, they project 2 excess cases of arrhythmia, 8 excess cases of ischemic heart disease, and 3 excess deaths due to ischemic heart disease.

Significant cardiovascular hazards were also identified in an observational study of 37,443 men diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration.[11] GnRH agonist therapy was associated with significantly increased risks for incident CHD (aHR 1.19; 95% CI 1.10 – 1.28), MI (aHR 1.28, 95% CI 1.08 – 1.52), sudden cardiac death (aHR 1.35; 95% CI 1.18 – 1.54), and stroke (aHR 1.22; 95% CI 1.10 – 1.36).

The results of a Canadian analysis of ADT-associated cardiac risks conflict with those of the previously described analyses. The authors reported no association between ADT and acute MI (HR 0.91, 95% CI 0.84 – 1.00) in their matched cohort study of men age ≥ 66 in an Ontario database.[16]

Retrospective analysis of the relatively smaller Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database of 3,262 men found that neoadjuvant ADT prior to prostatectomy was associated with excess cardiovascular mortality in the subset of men age ≥ 65 (adjusted HR 2.6; P = 0.002).[14] The CaPSURE analysis was limited by relatively few events (61 deaths) and failed to identify diabetes and coronary artery disease as risk factors for cardiovascular death.

Finally, analyses were carried out using a database of 5,077 men treated with radiation ± 4 months of ADT at a suburban cancer center. Those analyses found that an association between ADT and all-cause mortality after a median of 5.1 years of follow-up only in the subset of men who had a history of CAD-induced congestive heart failure or MI (26.3% vs. 11.2%, adjusted HR 1.96, 95% CI 1.04 – 3.71).[29]

Subheading: Post-hoc analyses of completed trials

These population-based observational studies prompted several post-hoc analyses of cardiovascular mortality among men who participated in prospective clinical trials. These analyses have largely found no association between GnRH agonist treatment and cardiovascular mortality.

Cardiovascular mortality was not significantly associated with ADT assignment in 3 large Radiation Therapy Oncology Group (RTOG) trials. RTOG 85-31 compared radiation alone to radiation with indefinite ADT in a group of over 900 men with prostate cancer.[6] After 117 cardiovascular-related deaths during 8.1 years of follow-up, there was no significant difference in cardiovascular mortality (8.4% with indefinite ADT, 11.4% when ADT was started only upon evidence of recurrence).[10] RTOG 86-10 compared radiation alone to radiation with 4 months of neoadjuvant combined androgen blockade in 456 men with prostate cancer. After 57 cardiovascular deaths during 10 years of follow-up, there was no significant difference in cardiovascular mortality (11% in the radiation-alone group, 14% in the combined therapy group).[30] RTOG 92-02 compared radiation with 4 months of GnRH agonist treatment with radiation with 28 months of GnRH agonist treatment in 1,554 men with prostate cancer. After 185 cardiovascular-related deaths during the 8.1 years of follow-up, there was no significant difference in cardiovascular mortality (5.9% with long-duration ADT, 4.8% with short duration ADT).[31]

Analysis of European Organization for Research and Treatment of Cancer (EORTC) trial 30891 found no difference in cardiovascular mortality based on the timing of ADT. In that trial, 985 men with prostate cancer were randomized to immediate ADT or deferred initiation of ADT upon symptomatic progression or serious complications.[32] After 185 deaths due to cardiovascular disease during 7.8 years of follow-up, there was no significant difference in cardiovascular mortality (17.9% with immediate ADT, 19.7% with deferred ADT). In another EORTC trial, 1,113 men were randomized to 6 months or to 3 years GnRH agonist treatment. After 5 years of follow-up, there was no significant difference in the incidence of fatal cardiac events (4.0% with 6 months of a GnRH agonist, 3.0% with 3 years of a GnRH agonist).[3]

In contrast, a pooled analysis of 3 completed trials of men undergoing radiation therapy with or without adjuvant ADT found that 6 months of ADT was associated with earlier-onset of fatal MI compared with no ADT, although this finding was only observed among men aged ≥ 65 years.[33] The small number of events (18 in the ADT group and 16 in the control group) limit the strength of these data.[34]

Subheading: Synthesis of CVD evidence

Taken together, these studies suggest that ADT is linked to modestly higher rates of cardiovascular morbidity. These studies have not established a causal relationship between ADT and cardiovascular disease. Most studies have reported no association between ADT and cardiovascular mortality. Potential explanations for conflicting results of different studies include selection biases of observational analyses, differences in populations studied (e.g. age, years of diagnosis and treatment, types of treatment), and other factors that are not well understood. Alternatively, these differences may reflect differences in the outcomes studied and the size of the populations studied. The observational studies predominantly assessed development of cardiovascular disease, which is infrequently fatal. Moreover, the magnitude of the association between GnRH agonist treatment and cardiovascular morbidity was modest. The ADT-attributable risk for myocardial infarction among existing positive studies was approximately 20%. Thus, the number of patients needed to demonstrate mortality differences in randomized controlled trials would be much larger than those in the relevant cancer treatment trials.[10, 30–33]

Discussion and Recommendations

Observational studies have consistently shown that GnRH agonist treatment is associated with elevated risk for the diagnosis of diabetes. The potential relationship between cardiovascular disease and GnRH agonists is less clear but has been suggested by a number of analyses. Coronary heart disease and type 2 diabetes are highly prevalent among older men in the general population and are among the most common causes of non-cancer death among patients with cancer.[35] Given this deepening appreciation for the metabolic and cardiovascular consequences of androgen deprivation, practical steps toward minimizing the impact of these changes are needed.

The AHA, ACS, and AUA together issued a science advisory on this topic.[17] In that advisory, they summarized the existing literature and concluded that there may be a relationship between ADT and cardiovascular events and death. They provided general recommendations for risk management including primary care physician monitoring of known coronary artery disease risk factors, educational information for primary care physicians regarding ADT-related risks, and adherence to existing guidelines for primary and secondary prevention of cardiac disease. They specifically recommend against ADT-prompted stress testing or cardiac catheterization.

That joint-organization advisory and the FDA safety announcement both make strong arguments for clinician judgment in balancing potential risks of GnRH agonist treatment against potential benefits. Given that the magnitude of any ADT-attributable effects on cardiovascular mortality is clearly modest, ADT should not be withheld from men who clearly stand to benefit from it. All the same, it is important to acknowledge that not all current GnRH agonist use is evidence-based. For example, GnRH agonists are commonly prescribed as primary therapy for localized disease.[36] Available data suggest that primary ADT is not beneficial and may actually be associated with worse survival.[37, 38]

For those whose prostate cancer does merit GnRH agonist treatment, GnRH antagonist treatment, or bilateral orchiectomy, there are no evidence-based guidelines for the management of ADT-induced risk for diabetes and CHD. For this population, it is reasonable to look to the evidence-based guidelines developed for the general population.

As ADT has clearly been shown to decrease insulin sensitivity[22, 23] and has been convincingly associated with type 2 diabetes, we believe that it is reasonable to consider men receiving ADT as being at high risk for the development of diabetes. The American Diabetes Association (ADA) recommends testing of hemoglobin A1C or fasting plasma glucose in patients with risk factors for diabetes.[39] Those with A1C ≥ 6.5% are diagnosed with diabetes while those with A1C 5.7 – 6.4% are considered highest risk for progression to diabetes. Those at highest risk should be re-tested yearly and counseled about effective strategies to reduce risks for both diabetes and cardiovascular disease. They should be counseled to pursue 5–10% weight loss and at least 150 minutes of weekly moderate physical activity (e.g. walking). Follow-up counseling is also important. In the general population, the Diabetes Prevention Trial showed that physical activity and weight loss led to a 58% reduction in the incidence of diabetes relative to control subjects, far greater than the reduction provided by drug therapy with metformin.[40]

Heart disease is the most common cause of mortality in the U.S. and is responsible for more than one fourth of all deaths.[41] In the general population, optimization of known risk factors is clearly associated with lower incidence of stroke and heart disease.[42, 43] We advocate a strong focus on primary prevention. This can be best achieved through intensive risk factor modification as guided by the adapted use of accepted guidelines from the AHA,[44] the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[45] and the ADA.[46]

Intensive risk factor modification can be achieved through several measures. Tobacco cessation and appropriate treatment of hypertension are essential. Weight control, regular physical activity, and reduced intake of saturated fat and cholesterol are all recommended. Aspirin may be appropriate for men with at least 10% ten-year risk of a first event due to CHD (e.g. by Framingham risk score), though its benefits must be weighed against an increased risk for major bleeds.[47] Hyperlipidemia should be managed with statins as first line drug therapy when lifestyle interventions do not achieve goal LDL cholesterol.

Diabetes and cardiovascular disease are prevalent and burdensome in the general population. ADT for prostate cancer is associated with an increased incidence of diabetes and may worsen risk for CHD and events. Prostate cancer survivors who receive this therapy are susceptible to these hazards. We advocate primary prevention through optimization of lifestyle and other modifiable risk factors. Careful attention to screening and treatment guidelines can likely combat the treatment-related hazards and improve overall health within this population.

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Key abbreviations

GnRH	Gonadotropin releasing hormone
ADT	Androgen deprivation therapy
FDA	Food and Drug Administration
MI	Myocardial infarction
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SEER	Epidemiology and End Results
CVD	Cardiovascular disease
SIR	Standardized incidence ratios
HR	Hazard Ratio
aHR	Adjusted hazard ratio
CHD	Coronary heart disease
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor

RTOG	Radiation Therapy Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
AHA	American Heart Association
ACS	American Cancer Society
AUA	American Urological Association
ADA	American Diabetes Association
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III

TABLE 1

Key points from the May 2010 FDA advisory

Health care professionals should be aware of these potential risks and carefully weigh the benefits and risks of GnRH agonists when determining a treatment for patients with prostate cancer.
Patients receiving a GnRH agonist should be monitored for the development of diabetes and cardiovascular disease.
Cardiovascular risk factors such as smoking and increases in blood pressure, cholesterol, blood sugar and weight should be managed according to current clinical practice.
Patients should not stop treatment with a GnRH agonist unless instructed to do so by a health care professional.